A YEAR AGO, I WENT TO COLLEAGUES AT THE Northwestern University Kellogg School of Business. I described a dilemma that I thought might make an interesting case study for their students and could be the subject for an editorial or commentary. A large pharmaceutical company, Genentech (South San Francisco, Calif), had developed a drug, bevacizumab (Avastin) for the treatment of cancer. The drug is an antibody against vascular endothelial growth factor A—which has been evaluated for the treatment of neovascular age-related macular degeneration.

Methods: In this multicenter, 2-year, double-blind, sham-controlled study, we randomly assigned patients with age-related macular degeneration with either minimally classic or occult (with no classic lesions) choroidal neovascularization to receive 24 monthly intravitreal injections of ranibizumab (either 0.3 mg or 0.5 mg) or sham injections. The primary end point was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months.

Results: We enrolled 716 patients in the study. At 12 months, 94.5% of the group given 0.3 mg of ranibizumab and 94.6% of those given 0.5 mg lost fewer than 15 letters, as compared with 62.2% of patients receiving sham injections ($p<.001$ for both comparisons). Visual acuity improved by 15 or more letters in 24.8% of the 0.3-mg group and 33.8% of the 0.5-mg group, as compared with 5.0% of the sham-injection group ($p<.001$ for both doses). Mean increases in visual acuity were 6.5 letters in the 0.3-mg group and 7.2 letters in the 0.5-mg group, as compared with a decrease of 10.4 letters in the sham-injection group ($p<.001$ for both comparisons). The benefit in visual acuity was maintained at 24 months. During 24 months, presumed endophthalmitis was identified in five patients (1.0%) and serious uveitis in six patients (1.3%) given ranibizumab.

Conclusions: Intravitreal administration of ranibizumab for 2 years prevented vision loss and improved mean visual acuity, with low rates of serious adverse events, in patients with minimally classic or occult (with no classic lesions) choroidal neovascularization secondary to age-related macular degeneration. (ClinicalTrials.gov number, NCT00056836.)

development of bevacizumab for ocular use. At that time, I talked to people at the Federal Trade Commission and lawyers familiar with the topic, and they agreed that Genentech was under no requirement to develop bevacizumab for the eye.

The October 5, 2006, issue of The New England Journal of Medicine contains an unprecedented number of AMD articles. There is a beautiful review of the pathophysiology of AMD by de Jong. Two articles describe the 1-year results of the clinical trials that led to FDA approval of ranibizumab. The bottom line of these studies is that this drug is clearly more efficacious than other presently available therapies for AMD, including photodynamic therapy with verteporfin and intravitreal use of triamcinolone or pegaptanib sodium (Macugen; Pfizer, New York, NY), also a VEGF inhibitor. In the 2 AMD trials, choroidal neovascularization, whether minimally classic, occult, or predominantly classic, responded dramatically to multiple intravitreal injections of ranibizumab, with approximately 95% of patients losing fewer than 15 letters at 1 year as compared with about 60% for sham injections or for photodynamic therapy.

In addition, unlike photodynamic therapy and pegaptanib use, improvement in visual acuity by 15 or more letters was seen in one quarter to one third of the patients treated with ranibizumab, as compared with only 5% of the sham-injection group and the photodynamic therapy group.

Notably, the adverse effects of ranibizumab were acceptable. Rare cases of endophthalmitis or uveitis were seen, and a low incidence of systemic thromboembolism was recorded. Although it has been suggested that VEGF may have a neuroprotective or trophic effect on the retina, and that the inhibition of all active isoforms of VEGF-A might be harmful, to date, this has not been reported clinically.

Most of the clinical trials with ranibizumab, including the 2 articles cited, have used monthly injections for up to 2 years. Some data exist to indicate that regimens that use fewer injections are less efficacious and that treatment in many cases might have to be continued for 2 years or even longer. The enormous cost of these injections (for a disease that is becoming more prevalent as the population ages) could put Centers for Medicare and Medicaid Services payments to physicians for other procedures at risk. If bevacizumab is proven equally effective as ranibizumab, the cost to Medicare, Medicare patients (for their deductible and copayments), patients without insurance, and patients in other parts of the world where treatment with ranibizumab is not fiscally feasible could be dramatically lowered.

It is clear that anti-VEGF therapy with ranibizumab or bevacizumab is now our best weapon against neovascular AMD. It is unclear whether combining it with other therapies such as photodynamic therapy or intravitreal corticosteroids might reduce the number of injections required. What is desperately needed is a head-to-head comparison of the efficacy and adverse consequences of bevacizumab and ranibizumab therapies. It seems unlikely that such a study will show that bevacizumab is superior to ranibizumab since the results with ranibizumab are so good. However, a study that shows equivalency would allow more affordable widespread use of anti-VEGF therapy. The National Eye Institute has announced its intention to fund a head-to-head comparison of bevacizumab and ranibizumab, but the results of this trial will not be available for 3 or 4 years. In the meantime, some physicians continue to use ranibizumab for AMD exclusively because of its FDA approval, and others continue to use bevacizumab because of its price. Some physicians are using both medications: for example, ranibizumab for Centers for Medicare and Medicaid Services–covered procedures and bevacizumab for patients where medical insurance does not cover treatment for diseases (other than AMD) for which ranibizumab is not FDA approved. This situation will persist until the National Eye Institute study is completed or a more effective therapy appears.

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REFERENCES